Fidgety movements in infants born very preterm: predictive value for cerebral palsy in a clinical multicentre setting

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Abstract: AIM: This study assessed predictive values of fidgety movement assessment (FMA) in a large sample of infants born very preterm for developmental abnormalities, in particular for cerebral palsy (CP) at 2 years in an everyday clinical setting. METHOD: This is a multicentre study of infants born preterm with gestational age lower than 32.0 weeks. FMA was performed at 3 months corrected age; neurodevelopment (Bayley Scales of Infant Development, 2nd edition) and neurological abnormalities were assessed at 2 years. Predictive values of FMA for the development of CP were calculated and combined with abnormalities at cerebral ultrasound. RESULTS: Five hundred and thirty-five infants (gestational age 28.2wks [standard deviation 1.3wks]) were included. Eighty-one percent showed normal fidgety movements and 19% atypical (82 absent, 21 abnormal) fidgety movements. Absent fidgety movements predicted CP at 2 years with an odds ratio (OR) of 8.9 (95% confidence interval [CI] 4.1-17.0), a combination of atypical fidgety movements and major brain lesion on cerebral ultrasound predicted it with an OR of 17.8 (95% CI 5.2-61.6). Mean mental developmental index of infants with absent fidgety movements was significantly lower (p=0.012) than with normal fidgety movements. INTERPRETATION: Detection of infants at risk for later CP through FMA was good, but less robust when performed in a routine clinical setting; prediction improved when combined with neonatal cerebral ultrasound.

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Fidgety movements in very preterm infants: predictive value for cerebral palsy in a clinical multicenter setting

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Abstract

Aim

This study assessed predictive values of fidgety movement assessment (FMA) in a large sample of very preterm infants for developmental abnormalities, in particular of cerebral palsy (CP) at 2 years in an everyday clinical setting.

Methods

This is a multicenter study of preterm infants with gestational age <32 0/7 weeks. FMA was performed at three months corrected age and neurodevelopment (Bayley Scales of Infant Development II) and neurologic abnormalities were assessed at 2 years. Predictive values of FMA for the development of CP were calculated and combined with abnormalities at cerebral ultrasound (cUS).

Results

535 infants (GA 28.2±1.3 weeks) were included. 81% showed normal FM and 19% atypical (82 absent, 21 abnormal) FM. Absent FM predicted CP at 2 years with an odds ratio (95%-CI) of 8.9 (4.1-17.0), a combination of atypical FM and major brain lesion on cUS predicted it with an odds ratio of 17.8 (5.2-61.6). Mean mental developmental index of infants with absent FM was significantly lower (p=0.01) than with normal FM.

Interpretation

Detection of infants at risk for later CP through FMA was good, but less robust when performed in a routine clinical setting; prediction improved when combined with neonatal cUS.

What this paper adds:

1. Fidgety movement assessment (FMA) in very preterm infants is practicable in a clinical setting, but results are less robust than when performed in highly skilled academic settings.
2. A combination of FMA and cerebral ultrasound appears to improve prognostic information.
3. FMA at 3 months of age can help to identify preterm infants at risk for cognitive dysfunction.

Introduction

Children born very preterm are at risk for impaired motor and cognitive development. Around 50% suffer from a broad range of neurodevelopmental impairment[1] and 10-20% have the characteristics of cerebral palsy[2]. At early age, standard neurological assessment has a low predictive value for neurological outcome[3]. Different neurodevelopmental assessments have been described that assess neuromotor function in early life in children at risk for later neurological problems[3]. In a systematic review summarizing the clinical properties of these assessment methods, Prechtl's Assessment of General Movements (GMs) showed the best predictive properties at an early age[3].

Prechtl developed this tool for evaluating the quality of spontaneous motility for the fetus and the young infant during the end of pregnancy and the first 4 months of life[4]. The method is based on observation of spontaneous motor activity during different maturational stages and provides information about the integrity of the nervous system at that age. Writhing movements (WM) are GMs that are observed already at preterm age, but best visible between term and 9 weeks; Fidgety movements (FM) can be seen from the 7th week, as soon as writhing movements gradually disappear, and persist to 16 weeks after term. Fidgety movement assessment (FMA) is a widely used method to assess spontaneous motor activity in young infants in order to predict developmental abnormalities at an early age. While FM abnormalities provide a more accurate prediction of later cerebral palsy than WM, the longitudinal evolution from writhing to fidgety period seems to be the best predictor for term- and preterm born infants. Atypical WM are associated with worse motor outcomes, while atypical FM associate worse motor outcome with poor cognitive and language performance at 2 and 4 years of age[5,9]. However, this method largely depends on professional experience and shows considerable intra- and inter-observer variability[6]. Few

reports have been published on its practicability and predictive value for a large sample of premature infants in a general clinical setting[5,7,8,9].

Therefore, the first aim of this prospective multicenter study was to determine the predictive values of FM at 3 months corrected age (CA) for the presence of CP in a large cohort of very premature children at 2 years CA. A second aim was to verify whether this method would also be applicable to, and robust in, an everyday clinical setting. A third aim was to look at predictive values of FMA when combined with cerebral ultrasound (cUS).

Method and Material

Study subjects

This multicenter study includes premature children born between $24^{0/7}$ and 31 6/7 weeks of gestation from 2004 to 2011 who participated in a national follow up program[10]. The three participating centers (Zurich, Bern and Geneva) performed general movement (GM) assessment in premature infants at 3 months CA, according to the Method of Prechtl [5,11]. Routine follow-up of very preterm infants at 2 years CA has been recommended and performed by the Swiss Neonatal Network and Follow-up Group, and follow-up data are prospectively collected and housed in the network database. Neonatal and follow-up data for this study were extracted from this prospective national database.

Data of GM assessment are not part of this prospective national database. Routine follow-ups of all three centers (to the present day) did not perform an examination on all very premature infants born before 32 weeks gestation at three months corrected age. The inclusion for fidgety movement assessment (FMA) for very premature infants, at corrected 3 months, was requested of parents, but was not mandatory. The incidence of infants with a GA below 32 weeks in the three participating centers was as follows: In center 1, infants were recruited between 2004 and 2011: 1166 very premature infants were born before 32

weeks gestation, 50 of which had malformations and 272 died: 295 of the remaining infants could be included in the study. In center 2, infants were recruited over the same time period; 1005 very premature infants were born, of which 56 with malformations and 143 died; in 184 FMA was done at the requested age to allow the inclusion. In center 3, recruitment took place between 2005 and 2007: 264 were born before 32 weeks gestation, 8 with malformations and 31 died: 57 could be included in the study.

Data collection and evaluation for this study were approved by the institutional ethical review boards of Zurich, Bern and Geneva and by the Swiss Federal Commission for Privacy Protection in Medical Research. Participating centers were obliged to inform parents about the scientific use of anonymized data.

Definition of neonatal variables

Birth weight z-scores were calculated based on the growth curves[12]. Major brain lesion was defined by cUS examination between birth and term as intraventricular haemorrhage (IVH) greater than grade 2, according to the classification of Papile[13], and/or cystic periventricular leukomalacia[14]. Bronchopulmonary dysplasia was defined as additional oxygen requirements at $36^{0/7}$ weeks postmenstrual age[15]. Retinopathy of prematurity was defined using the International Committee criteria[16]. Necrotising enterocolitis was defined as pneumatosis intestinalis or pneumatosis vena portae (Bell's stage II) or higher[17]. The presence or absence of infection was classified as uninfected, suspected (clinical and laboratory signs of sepsis but absence of positive blood or cerebrospinal fluid culture), and proven sepsis (positive blood or cerebrospinal fluid culture)[18].

Socioeconomic status (SES) was estimated using a validated 12-point socioeconomic score based on maternal education and paternal occupation and was classified into: higher class (score 2-5), middle class (6-8) and lower class (9-12)[19].

General Movement Assessment at three months corrected age

General Movement assessment was performed as described previously by pediatric physical therapists, child neurologists, or developmental pediatricians who have successfully completed formal training in Prechtl's method, depending on center preferences. The child had to lie in supine position, although he or she was allowed to turn on one side. Spontaneous movements were only assessed in Prechtl's behavioral state 4 (eyes open, not crying, irregular respiration, movements present)[11].

General Movements were classified based on visual *Gestalt* perception intended to capture the integrity of the movement with its complexity, variation, and fluency; providing information on the integrity of the nervous system. For the present study, only assessments during the fidgety period were included. FM were classified as either normal, as described, or atypical, defined as follows: abnormal, i.e. FM whose amplitude, speed and jerkiness were moderately or greatly exaggerated; or absent, i.e. FM were not observed[11].

Outcome assessment at 2 years corrected age

Neurodevelopmental examination was routinely performed by experienced developmental pediatricians or neuropediatricians at 18–24 months CA at each of the three Neonatal Follow-up centers. The assessment consisted of a clinical examination, a structured neurological assessment and a developmental assessment using the Bayley Scales of Infant

Development. 2nd edition (BSID-II)[20]. Infants who were severely impaired and a structured test with the BSID-II could not be performed were assigned a mental development index (MDI) and psychomotor development index (PDI) of 49. Cerebral palsy was diagnosed and classified according to the guidelines of the Surveillance Group of CP in Europe[21]. Functional performance was defined according to the Gross Motor Functioning Classification Scale (GMFCS)[22].

Statistical Analysis

We first used Chi-square-, independent T-, and Mann-Whitney U-test to compare baseline characteristics (perinatal characteristics, neonatal morbidities, socio-economic status, and CA at fidgety period) between infants with normal and absent FM, and between infants with normal and atypical FM. We then used regression models to compare dichotomous and continuous outcome measures (CP, MDI, PDI, and MDI or PDI value below - 2SD) between infants with normal and absent FM, and between infants with normal and atypical FM. We then went on to estimate the association between FM at 3 months and neonatal cUS findings (that is a) absent FM, b) absent or abnormal FM, c) major brain lesion, and d) major brain lesion and absent or abnormal FM) with the development of CP at 2 years using uni- and multivariable logistic regression models. Models were adjusted for the following variables: lower socio-economic status (i.e. score above 8), GA below 28 weeks, male sex, bronchopulmonary dysplasia, sepsis/necrotising enterocolitis, retinopathy of prematurity, and major brain lesion, based on their association with neurodevelopmental outcome[18]; and 'study center', because of the known center-to-center differences in neonatal outcomes in the Swiss perinatal popualtion[23].

Associations were given as odds ratios (OR) with 95%-confidence intervals (95% CI). Finally, sensitivity, specificity, positive and negative predictive values, and their 95%

confidence intervals were calculated for: 1) absent FM; 2) atypical, i.e. absent or abnormal FM; 3) major brain lesion in the neonatal cerebral ultrasound; and 4) the combined observation of atypical FM and major brain lesion for the development of CP at 2 years of age. Analysis were performed using SPSS v.21.0 (IBM Corp., Armonk, NY, USA); the significance threshold was defined as $p < 0.05$, testing was 2-sided.

RESULTS

Study population

Data on 535 study infants were available from the three participating centers: 55% female; mean (range) GA 28.2 (23.9-31.9) weeks; mean (range) birth weight 1023 (380-1600). Among them, 432 (81%) showed normal FM at a mean CA of 13.0±3.1 weeks, 81 (15%) infants showed no FM, and 21 (4%) infants showed abnormal FM (Table 1). The average (range) CA at FM evaluation was similar between groups: normal FM at 13.1 (12.0 – 20.0) weeks; abnormal FM at 12.1 (12.0 – 16.0) weeks; absent FM at 12.8 (12.0 – 20.0) weeks.

Infants with absent FM had significantly lower gestational ages ($p=0.02$) (Table 1). Out of all neonatal morbidities, infants with absent FM suffered significantly more often from retinopathy of prematurity ($p=0.02$) and IVH grade 1 ($p<0.001$), albeit not for grades 2, 3, and 4 IVH; though not so for cystic periventricular leukomalacia (PVL); however, the number of children with PVL was rather small. Baseline characteristics of infants with normal and atypical FM were similar except for the rates of IVH grade 1 and major brain lesion, which were significantly higher in infants with atypical FM than in infants with normal FM ($p = 0.01$ and < 0.01, respectively). Astonishingly, periventricular flaring in the cUS at day 14 of life or later was found much more frequently in the group of children with normal FM compared to absent FM ($p=0.003$); this flaring was not at all predictive of a negative outcome,

but rather presented more randomly in the population we studied. (table 1).

Outcome at 2 years corrected age (tables 2 and 3a and b)

In order to achieve a more complete picture, despite the very low number of infants with "abnormal fidgety movements", we also performed analyses for normal, abnormal, absent, and "atypical" (abnormal and absent) fidgety movement patterns. However, due to the low number of infants with abnormal FM, this group is not visible in tables 2, 3 a/b and 4.

Outcome assessment took place at an average (range) CA of 23.4 (18.0 – 38.0) months. Among all study infants, 39 (7%) infants suffered from CP at the CA of 2 years. Bilateral spastic CP (n = 22) was the most frequent of all forms of CP, followed by unilateral spastic- (n = 11), ataxic- (n = 5), and dyskinetic (n = 1) CP. Among the 39 infants with CP, absent FM was identified in 20, and abnormal FM was identified in 3; while 16 infants had normal FM. Infants with a GMFCS level above 2 (n= 8) had absent FM in 7 and normal FM in 1 case. Of 535 study infants, 80 had atypical, i.e. absent or abnormal FM and did not develop CP. Table 2 details the data concerning type and grading of CP.

Infants with absent FM ($p<0.001$) and abnormal FM ($p=0.03$) were significantly more likely to develop CP than infants with normal FM. Both results remained statistically significant after adjustment for confounders ($p<0.001$ and $p=0.04$, respectively). Mean (SD) MDI of infants with absent FM (86.6, 18.5) was significantly lower ($p=0.01$) than in infants with normal FM (92.4, 16.6). Accordingly, the rate of infants with an MDI < 70 (i.e. -2SD) was higher in infants with absent FM than in infants with normal FM ($p=0.02$). After adjustment

for confounders, the level of significance for both comparisons became marginal (p=0.08 and 0.05, respectively) (Table 3a).

When we excluded those infants who developed CP, the association with MDI became weaker; nevertheless, significant associations of low mean PDI with major brain lesions ($p<0.005$) and with major brain lesions and absent or abnormal FM ($p<0.001$) were found; an effect which disappeared as soon as the value was adjusted (table 3b).

Both the presence of major brain lesion in the neonatal cUS examination (OR 8.4, 95%-CI 3.8 – 18.4) and the absence of FM at 3 months of CA (OR 8.9, 95%-CI 4.1 – 17.0) were strongly associated with the later development of CP ($p < 0.001$). The observation of atypical, i.e. absent or abnormal FM, despite its strong association with CP (OR 7.5, 95%-CI 3.8 – 14.8), did not increase the OR for later CP, while the combined observation of major brain lesion and atypical, i.e. absent or abnormal, showed the strongest association (OR 17.8, 95%-CI 5.1 – 61.58) with CP.

Predictive values of FM for the development of cerebral palsy (table 4)

Table 4 shows details of the calculated predictive values. Absent FM provided the highest sensitivity (56%) for later CP compared to major brain lesion (31%) while the combined observation of atypical FM and major brain lesion provided the lowest value (15%).

Specificity value was best provided by the combined observation of atypical FM and major brain lesion (99%), while absent FM provided the lowest value (87%). The true negative rate ranged from 94% (combined atypical FM and major brain lesion) to 96% (absent FM), while the true positive rate ranged from 24% (absent FM) to 54% (combined atypical FM and major brain lesion).

Positive predictive value reached 54% for the combined observation of atypical FM and major brain lesion and was below 33% for the other assessments. All assessments provided a

negative predictive value above 93%. The observation of abnormal FM combined with absent FM provided no further increase of predictive values.

We observed that the positive and negative predictive values were similarly low (≤ 31%) and high (≥ 92%), respectively, in all study centers, while relevant differences in the sensitivity (range 42% - 100%) and specificity (range 67% - 96%) among centers were noticed.

Discussion

This multicenter study, consisting of 535 premature children born before 32 weeks of gestation, assessed the predictive value of FMA for CP and cognitive outcome in combination with cerebral ultrasound. Circumstances of the study reflected daily practice in the routine follow-ups of former premature children within the context of the Swiss Neonatal Network and Follow-up Group. To our knowledge, the present study has the largest sample size of very preterm infants with FMA.

In summary, the results of the study demonstrate that very preterm children with absent FM or atypical (absent and abnormal merged together) FM were significantly more likely to develop CP than those with normal FM, a finding in line with previous studies[4,5,11]. After adjustment for several risk factors of poor neurodevelopmental outcome, the association between absent or abnormal FM and later CP remained significant and was clinically relevant. Major brain lesions were also clearly associated with CP, and when combined with atypical FM, the effect became even stronger.

Predicting CP in former premature infants is of great importance for parental counseling and support planning. In our study population, the incidence of CP was 7%, in line with previous studies[24]. The sensitivity of absent FM for the development of later CP was 56%. Thus, in this sample and under the described clinical setting only half of the children who develop CP would be detected with the help of FM assessment at 3 months CA. In addition to the

prediction of CP later in life, the severity and distribution of later motor handicap is also relevant. In the present study, absent FMs were more frequently associated with severe functional impairment. However, the subgroups of GMFCS were too small to calculate a predictive value of FM for the severity of motor abnormalities, and further research on larger numbers would be valuable.

The combined observation of major brain lesion observed in neonatal cUS and atypical FM (absent and abnormal FM merged together) at 3 months showed the strongest association with later CP. These findings underline the hypothesis that FMA improves prediction and is best used in conjunction with other methods. We, therefore, strongly recommend combining the FMA with earlier neuro-imaging for parental counseling and therapeutic plans.

We showed that absent as well as atypical FMs were associated with poorer cognitive outcome. An association between general movements and later cognitive development in preterm infants at preschool and school age has also been previously reported [5,6,8,9]. In addition to these previous studies, our results underline that atypical spontaneous motor activity at an early age might not only be predictive for motor, but also for cognitive development. Why absent and atypical FMA is associated with poorer cognitive outcome can only assumed, as to date no causative explanation is reported in the literature.

In former premature children, minor motor impairments are common[25]. Although minor motor impairments are not by definition compatible with the diagnosis of CP, they still have a considerable impact on quality of life, academic achievement and participation[25]. Minor motor impairments in former premature children may or may not be associated with cognitive impairments. In our detection of atypical FM at 3 months CA, we may have additionally identified infants with minor motor impairments. As CP and minor motor deficits are often associated with cognitive problems, it might be possible that what we observed is of epiphenomenal nature, reflecting a common implication of brain areas involved in both

cognitive and motor performance. Our study does not allow a definite conclusion to whether atypical FM at 3 months of age are an expression of motor, cognitive, or the combination of motor and developmental abnormalities later in life. However, our findings highlight that FMA may also identify preterm infants at risk of cognitive dysfunction and that, a thorough motor and cognitive follow up is therefore important.

In comparison to previous studies using similar techniques[26], the sensibility of FMA to detect later CP was low in the present study. Specificity on the other hand was high and comparable to previously reported results[7]. Most of the previous studies were conducted by experts on GM. In the present study, FMs were assessed by certified professionals that use FMA only as part of their daily clinical practice. It was previously reported that inter-rater and intra-rater agreements of FMA differ considerably depending on experience[6]. Therefore, rater differences may explain the higher sensitivity of previous studies. The findings of the present study remind us that methods developed and applied by experts in highly skilled academic settings may be less robust when applied in a daily clinical setting.

The present study illustrates that FMA, even in a daily clinical setting, is a valuable tool to detect in very premature infants an increased risk of CP. However, the interpretation of the results needs caution. We have shown that the predictive value can be improved in combination with cerebral ultrasound, and therefore recommend that the results of cerebral ultrasound and FMA be combined for increased accuracy.

A weakness of this study is the relatively low inclusion percentage of very premature infants for FMA. Routine follow-ups of all three centers (to the present day) did not perform an examination on all very premature infants born before 32 weeks of gestation at three months corrected age.

Finally, results from the group with "abnormal fidgety movements" corroborated those from previously reported studies, where this particular movement pattern: a) is much less often observed than that of absent fidgety movements, and b) provides lower prediction than absent fidgety movements[6].

The major limitation of the present study is that three different teams scored FM independently. Nevertheless, the rater trainings were comparable as all three teams used the guidelines for the GM assessment previously published [11].

Outcome testing with the BSID-II, however, were not in all cases performed by different teams or different persons within the same team, but not simultaneously. Furthermore, as motor patterns may change considerably in toddlers and young children with neurological abnormalities, the diagnosis of CP at 2 years of age is generally considered early. The classification of subtypes and GMFCS levels is particularly difficult at this early age. The guidelines of the Surveillance Group of Cerebral Palsy in Europe used to define CP in the present study, recommend that a definite diagnosis of CP should be undertaken at the age of 4 years. Minor neurological and cognitive deficits might not be visible at the age of 2 years. The BSID-II score did reveal minor deficits in patients with an absence of CP; but BSID-II does not provide a good predictive value for later cognitive outcome[5], and children with normal cognitive test scores at 2 years of age might later still reveal minor deficits.

Conclusion

In a daily clinical setting, FMA at 3 months of age is easy to perform for trained staff, non-invasive and cost-effective. However, the predictive value of FM in daily clinical practice is less robust than shown in highly skilled academic settings. When FMA is combined with cUS, however, its sensitivity in predicting CP increases. In conclusion, additional diagnostic

tools, such as cUS, are recommended to improve the predictive power of FMA in every day clinical settings.

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Abbreviations

BSID-II	Bayley Scales of Infant Development 2nd edition
CA	Corrected age
CP	Cerebral palsy
cUS	cerebral ultrasound
FM	Fidgety movements
GM	General movements
GMFCS	Gross Motor Function Classification System
IVH	Intraventricular hemorrhage
MDI	Mental developmental index
PDI	Psychomotor developmental index

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Authors' contributions
Drs AD, SG and GN conceptualized and designed the study, coordinated and supervised data collection at each site, drafted the initial manuscript, and approved the final manuscript as submitted.
MF, IB, CBT, CUQ, BP did the data acquisition and data analysis.
Drs MN, PSH, CM, REP, HUB, BL, MS reviewed and revised the manuscript, and approved the final manuscript as submitted.

References

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood *Lancet.* 2008 Jan 19;371(9608):261-9
2. Aylward GP, Neurodevelopmental outcomes of infants born prematurely, *J Dev Behav Pediatr.* 2014 Jul-Aug;35(6):394-407
3. Spittle AJ, Doyle LW, Boyd RN. A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life. *Dev Med Child Neurol.* 2008 Apr;50(4):254-66
4. Prechtl HF. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction *Early Hum Dev.* 1990 Sep; 23(3):151-81
5. Spittle AJ, Spencer-Smith MM, Cheong JL, Eeles AL, Lee KJ, Anderson PJ, Doyle LW. General movements in very preterm children and neurodevelopment at 2 and 4 years *Pediatrics.* 2013 Aug;132(2):e452-8
6. Bernhardt I, Marbacher M, Hilfiker R, Radlinger L. Inter- and intra-observer agreement of Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants. *Early Hum Dev*. 2011 Sep;87(9):633-9
7. Spittle AJ, Cheong J, Doyle LW, Roberts G, Lee KJ, Lim J, Hunt RW, Inder TE, Anderson PJ Neonatal white matter abnormality predicts childhood motor impairment in very preterm children *Dev Med Child Neurol.* 2011 Nov;53(11):1000-6.
8. Bruggink JLM, van Braeckel KN, and Bos AF. The early motor repertoire of children born preterm is associated with intelligence at school age. *Pediatrics* 2010, 125, e1356–e1363.
9. Einspieler C, Bos AF, Libertus ME, Matschik PB. The general movement assessment helps us to identify preterm infants at risk for cognitive dysfunction. *Frontiers in Psycholgy*. 2016 March;406(7):1-8.
10. Schlapbach LJ, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, Bickle-Graz M, Bucher HU, Latal B, Natalucci G; Swiss Neonatal Network & Follow-up Group. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. *BMC Pediatr.* 2012 Dec 28;12:198
11. Einspieler C, Prechtl HF Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system *Ment Retard Dev Disabil Res Rev.* 2005;11(1):61-7
12. Voigt M, Fusch C, H. OD, Hartmann K, Rochow N, Renken C, Schneider KTM: Analysis of the Neonatal Collective in the Federal Republic of Germany 12th Report: Presentation of Detailed Percentiles for the Body Measurements of Newborns. *Geburtsh Frauenheilk* 2006, 66:956-970.
13. Papile LA, Munsick-Bruno G, Schaefer A: Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. *J Pediatr* 1983, 103(2):273-277.
14. de Vries LS, Eken P, Dubowitz LM: The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992, 49(1):1-6.
15. Jobe AH, Bancalari E: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001, 163(7):1723-1729.
16. The International Committee for the Classification of Retinopathy of Prematurity: The International Classification of Retinopathy of Prematurity revisited. *Archives of Ophtalmology* 2005, 123(7):991-999.

17. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T: Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978, 187(1):1-7.
18. Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, Nelle M, Bucher HU, Latal B, for the Swiss Neonatal Network and Follow-Up Group: Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics* 2011, 128(2):e348-357.
19. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G: Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. *Dev Med Child Neurol* 1989, 31(4):440-456.
20. Bayley N: Bayley Scales of Infant Development. 2nd edition. San Antonio (TX): *The Psychological Corporation; 1993*.
21. Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev Med Child Neurol.* 2000 Dec;42(12):816-24.
22. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997 Apr;39(4):214-23
23. Steurer MA, Adams M, Bacchetti P, Schulzke SM, Roth-Kleiner M, Berger TM; Swiss Neonatal Network. Swiss medical centres vary significantly when it comes to outcomes of neonates with a very low gestational age. *Acta Paediatr.* 2015 Sep;104(9):872-9.
24. Sellier E, Platt MJ, Andersen GL, Krägeloh-Mann I, De La Cruz J, Cans C; Surveillance of Cerebral Palsy Network. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. *Dev Med Child Neurol.* 2016 Jan;58(1):85-92.
25. Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. *Semin Fetal Neonatal Med*. 2014 Apr;19(2):84-9.
26. Oberg GK, Jacobsen BK, Jorgensen L. Predicitve Value of General Movement Assessment for Cerebral Palsy in Routine Clinical Practice. *Phys.Ther.* 2015 Nov;95(11):1469-95

Table 1: Baseline characteristics of infants with normal, absent, and abnormal fidgety movements.

mean (range) n (%)		Normal FM n = 432 (81%)	Abnormal FM n = 21 (4%)	Absent FM n = 82 (15%)
Perinatal characteristics				
Sex (female)		230 (53%)	13 (62%)	51 (62%)
Gestational Age (weeks)		28.3 (23.9 – 31.9)	27.9 (25.0 – 31.9)	27.8 (24.4 – 31.9) [1]
Birth Weight (grams)		1035 (460 – 1600)	950 (405 – 1490)	990.0 (380 – 1500)
Head circumference		26.1 (22.1 – 29.3)	25.2 (25.0 – 30.5)	25.8 (22.0 – 27.8)
Antenatal corticosteroids		376 (87%)	10 (48%)	75 (91%)
Multiple pregnancy		120 (28%)	3 (14%)	21 (26%)
Neonatal morbidities				
Bronchopulmonary dysplasia		65 (15%)	4 (19%)	14 (17%)
Sepsis		77 (18%)	5 (24%)	7 (8%)
Necrotising enterocolitis		9 (2%)	1 (5%)	2 (2%)
Retinopathy of prematurity, grade > 2		16 (4%)	3 (14%)	3 (4%)
Patent ductus arteriosus		188 (43%)	10 (48%)	35 (43%)
Major brain lesion		26 (6%)	5 (24%) [2]	6 (7%)
Intraventricular haemorrhage	1	19 (4%)	5 (24%) [3]	13 (16%) [4]
	2	42 (10%)		6 (7%)
	3	15 (3%)	3 (14%)	2 (2%)
	4	5 (1%)	0	1 (1%)
Periventricular flaring > 14 days		133 (31%)	1 (5%) [5]	12 (15%) [6]
Cystic periventricula leukomalacia		16 (4%)	2 (9%)	3 (4%)
Socio-economic status		5.5 (2 – 12)	5.8 (2 – 12)	6.1 (2 – 11)
Corrected age at fidgety period		13.1 (12.0 – 20.0)	12.1 (12.0 – 13.0)	12.8 (12.0 – 20.0)

FM, fidgety movements. Baseline characteristics of infants with normal FM (reference) are compared with those of infants with abnormal FM [2) OR (95%.CI) 4.9 (1.7 ; 14.4), p = 0.010; 3) OR (95%-CI) 3.4 (1.2 ; 9.9), p = 0.032; 5) OR (95%-CI) 0.1 (0.1 ; 0.9), p = 0.021], and those of infants with absent

FM [1) Mean difference (95%-CI) -0.5 (-1.0 ; -0.1), p = 0.022; 4) OR (95%-CI) 2.1 (1.0 ; 4.1), p = 0.041; 6) OR (95%-CI) 0.5 (0.3 – 0.9), p = 0.046)]

The interpretation of the abnormal FM was problematic because its small number.

Table 2 Neuromotor outcome at 2 years in infants with normal, abnormal and absent FM's

	Normal FM **n = 432**	**Absent FM** **n = 82**	**Total**
No cerebral palsy	416/432 (96%)	62/82 (76%)	496/535 (93%)
Cerebral Palsy	16/432 (4%)	20/82 (24%)	39/535 (7%)
Unilateral Spastic cerebral palsy	5	6	11/39
Bilateral Spastic cerebral palsy	9	12	22/39
Dyskinetic cerebral palsy	0	1	1/39
Ataxic cerebral palsy	2	1	5/39
GMFCS 1	7	6	16/39
GMFCS 2	7	8	15/39
GMFCS 3	1	3	4/39
GMFCS 4	0	4	4/39
GMFCS 5	0	0	0

The group of infants with abnormal FM has been removed due to its small number.

Table 3a: Predicion of neurodevelopmental outcome at 2 years of corrected age of infant with normal, abnormal, and absent FM; of infants with major brain lesions on neonatal brain ultrasound, and of infants of both major brain lesions and atypical FM.

	Normal FM n = 432	**Absent FM n = 83**		**Major brain lesion n = 35**		**Major brain lesions and absent or abnormal FM n = 11**	
OR (95% CI); B (95% CI)	n (%) mean (range)	n (%) mean (range)	Unadjusted Adjusted *	n (%) mean (range)	Unadjusted Adjusted **	n (%) mean (range)	Unadjusted Adjusted **
CP, n (%)	16 (4%)	20 (24%)	8.9 † (4.1 ; 17.1) 10.9 † (4.2 ; 28.0)	12 (34%)	8.4 † (3.8 ; 18.5) 8.4 † (3.3 ; 21.8)	6 (54%)	17.8 † (5.2 ; 61.6) 31.1 † (4.4 ; 222.0)
MDI ≤ 70, n (%)	34 (8%)	13 (16%)	2.4 (1.2 ; 4.9) 2.9 (1.1 ; 7.2)	7 (20%)	3.2 # (1.3 ; 7.9) 4.0 ¶ (1.4 ; 11.1)	1 (9%)	1.6 (0.2 ; 13.4) N.A.
PDI ≤ 70, n (%)	56 (13%)	9 (11%)	1.0 (0.4 ; 2.5) 1.7 (0.6 ; 5.1)	6 (17%)	2.3 (0.9 ; 6.0) 2.2 (0.8 ; 6.2)	3 (27%)	23.9 ¶ (2.4 ; 234.1) N.A.
MDI, mean (SD)	92.4 (16.6)	86.6 (18.5)	-5.4 # (-9.6 ; -1.2) -4.8 # (-9.3 ; -0.3)	86.6 (10.1)	-4.8 (-11.1 ; 1.4) -4.4 (-11.1 ; 2.2)	87.0 (19.1)	-5.0 (-17.6 ; 7.6) -0.6 (-15.4 ; 14.2)
PDI, mean (SD)	88.1 (14.9)	86.3 (16.0)	-2.2 (-6.5 ; 2.2) -4.1 (-8.7 ; 0.4)	63.0 (18.2)	-7.5 # (-13.4 ; -1.6) -7.5 # (-13.7 ; -1.4)	80.6 (18.3)	-24.8 ¶ (-39.7; -10.0) -28.0 ¶ (-45.1; -11.1)

CP, cerebral palsy; OR, odds ratio, 95% CI, 95% confidence interval; B, B coefficient of linear regression model; MDI, mental development index; PDI, psychomotor development index; FM, fidgety movements; *, adjusted for study center, low socio-economic status, gestational age below 28 weeks, gender, bronchopulmonary dysplasia, sepsis/necrotising enterocolitis, retinopathy of prematurity > 2 grade, and major brain lesion; **, adjusted for study center, low socio-economic status, gestational age below 28 weeks, gender, bronchopulmonary dysplasia, sepsis/necrotising enterocolitis, retinopathy of prematurity > 2 grade; †, $p < 0.001$; ¶, $p < 0.01$; #, $p < 0.05$.

The group of infants with abnormal FM has been removed due to its small number.

Table 3b: Predicion of neurodevelopmental outcome at 2 years of corrected age of infant without CP with normal, abnormal, and absent FM; of infants with major brain lesions on neonatal brain ultrasound, and of infants of both major brain lesions and pathological FM.

	Normal FM **n = 392**	**Absent FM** **n = 57**		**Major brain lesion** **n = 20**		**Major brain lesions and absent or abnormal FM** **n = 2**	
OR (95% CI); B (95% CI)	n (%) mean (range)	n (%) mean (range)	Unadjusted Adjusted *	n (%) mean (range)	Unadjusted Adjusted **	n (%) mean (range)	Unadjusted Adjusted **
MDI ≤ 70, n (%)	33 (8%)	8 (14%)	1.8 (0.8 ; 4.1) 1.7 (0.6 ; 4.7)	6 (30%)	5.0 ¶ (1.8 ; 13.7) 6.2 ¶ (2.1 ; 18.2)	0	N.A. N.A.
PDI ≤ 70, n (%)	38 (10%)	2 (3%)	0.4 (0.1 ; 1.7) 0.2 (0.0 ; 1.6)	6 (30%)	1.7 (0.5 ; 5.9) 1.5 (0.4 ; 5.8)	1 (50%)	1.0 (0.9 ; 1.1) N.A.
MDI, mean (SD)	92.5 (16.7)	89.4 (17.9)	-2.4 (-1.6 ; 7.7) -3.1 (-8.2 ; 1.9)	86.6 (10.1)	-4.8 (-11.1 ; 1.4) -4.6 (-12.3 ; 3.1)	87.0 (19.1)	-5.0 (-17.6 ; 7.6) 4.1 (-19.0 ; 27.2)
PDI, mean (SD)	88.4 (14.6)	89.4 (13.2)	1.1 (-3.5 ; 5.5) -0.9 (-5.8 ; 3.9)	63.0 (18.2)	-7.5 # (-13.4 ; -1.6) -5.3 (-12.1 ; 1.5)	80.6 (18.3)	-24.8 ¶ (-39.7; -10.0) -18.2 (-46.6 ; 10.1)

#, $p < 0.05$;¶, $p = 0.001$

CP, cerebral palsy; OR, odds ratio, 95% CI, 95% confidence interval; B, B coefficient of linear regression model; MDI, mental development index; PDI, psychomotor development index; FM, fidgety movements; *, adjusted for study center, low socio-economic status, gestational age below 28 weeks, gender, bronchopulmonary dysplasia, sepsis/necrotising enterocolitis, retinopathy of prematurity > 2 grade, and major brain lesion; **, adjusted for study center, low socio-economic status, gestational age below 28 weeks, gender, bronchopulmonary dysplasia, sepsis/necrotising enterocolitis, retinopathy of prematurity > 2 grade; †, $p < 0.001$; ¶, $p < 0.01$; #, $p < 0.05$.

The group of infants with abnormal FM has been removed due to its small number.

Table 4: Predictive values for cerebral palsy at 2 years of corrected age

Predictive values	Absent FM	Major brain lesion	Major brain Lesion and absent or abnormal FM
Sensitivity 95% CI	**56%** 38% - 72%	**31%** 17% - 46%	**15%** 6% - 31%
Specificity 95% CI	**87%** 84% - 90%	**95%** 93% - 97%	**99%** 97% - 100%
PPV 95% CI	**24%** 16% - 32%	**32%** 18% - 50%	**54%** 24% - 82%
NPV 95% CI	**96%** 94% - 98%	**95%** 92% - 96%	**94%** 91% - 96%

FM, fidgety movements, CI, confidence interval, PPV, positive predictive value, NPV, negative predictive value, AUROC, area under the receiver operating characteristic curve ($p < 0.001$ for all 4 values).
The group of infants with abnormal FM has been removed due to its small number.